In Utero DETECTION OF FETAL ALCOHOL SYNDROME USING ULTRASONOGRAPHY

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In Utero Detection of Fetal Alcohol Syndrome Using Ultrasonography

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ABSTRACT

***IN UTERO* DETECTION OF FETAL ALCOHOL SYNDROME USING ULTRASONOGRAPHY**. Chloe Lynne Thio and Richard R. Viscarello. Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, CT.

A characteristic consequence of alcohol consumption during pregnancy is fetal alcohol syndrome (FAS) which is characterized by growth deficiency, intellectual impairment, developmental delay, and craniofacial anomalies. The purpose of this study is to test the utility of combining the T-ACE questionnaire, which detects 76% of alcoholics, with prenatal ultrasonography for detection of FAS *in utero*.

We administered the T-ACE questionnaire to a sample of 265 gravid women at three different sites. Ultrasonographic measurements of the mid-face and the cavum-thalamic-cerebellar axis were performed at three gestational age ranges: 16-19, 24-28, and 32-35 weeks.

The overall percentage of women whose fetuses were at risk for developing FAS, T-ACE positive women, was 30.1%. There was a tendency for head circumference, inner orbital diameter, mid-orbital to mid-upper lip distance, outer orbital to mid-upper lip distance, and cerebellar and thalamic measurements to be smaller in "at risk" fetuses at 16-19 and 24-28 weeks. Head circumference at 16-19 weeks and cerebellar and thalamic measurements in the 24-28 week range were statistically significant as compared to the control group at p=.05, p=.003, and p=.03 levels respectively. A four chamber view of the heart was visualized in all fetuses. Two fetuses, whose mothers drank large quantities of alcohol throughout pregnancy and were noted to have abnormal cephalometry by ultrasound at 16 and 24 weeks, were subsequently determined to have characteristics consistent with FAS at birth.

This study suggests that the distinct craniofacial morphometry characterizing FAS may be detectable *in utero* prior to the third trimester using sonography. Since the most severe neurological consequences of FAS may occur in the third trimester and since

alcoholic women who receive intensive counseling can significantly reduce their drinking prior to the third trimester, the combination of early prenatal detection and appropriately directed counseling may allow for secondary prevention of the deleterious effects of alcohol on the developing nervous system.

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INTRODUCTION

The teratogenic effects of alcohol have been recognized since Biblical times as evidenced by a passage from Judges 13:7: "Behold, thou shalt conceive, and bear a son; now drink no wine or strong drink." In 1899, Sullivan first reported a link between alcohol and its effects on the fetus when he noted that female drunkards in a Liverpool jail had an infant death and stillbirth rate more than double that of their non-alcoholic relatives (Streissguth and al 1980). These findings received little attention until 1968 when Lemoine, a French physician, first documented his observations of the pattern of abnormalities seen in children born to alcoholic mothers (Lemoine et al. 1968). He studied 120 children born of alcoholic parents and noted growth deficiency, behavioral disturbances, and specific patterns of malformation.

In 1970, Ulleland noted growth deficiencies in ten offspring of alcoholic mothers (Ulleland et al. 1970). In eight of these ten children, Jones and Smith (1973) recognized a characteristic pattern of craniofacial, limb, and cardiovascular anomalies coining the term fetal alcohol syndrome (FAS) (Jones et al. 1973). Their description, which remains accurate today, included the following constellation of characteristics. Growth delay was seen in length, weight, and head circumference. Craniofacial anomalies were present including short palpebral fissures, maxillary hypoplasia, short nose, short philtrum, and microcephaly. Development was delayed with deficits in fine and gross motor skills. Cardiac anomalies such as atrial septal defect, ventricular septal defect, and patent ductus arteriosus were noted; the incidence of these cardiac defects was variable. Later that same year, Jones and Smith reported three additional cases with similar malformations (Jones and Smith 1973). After ten years of follow-up, eight of these eleven children were still alive and all of them exhibited growth deficiencies and retained their craniofacial dysmorphology (Streissguth, Clarren, and Jones 1985). Four were of borderline intelligence and four were severely intellectually-handicapped. The degree of mental

impairment was directly related to the severity of the craniofacial malformations and to the extent of growth deficiency.

Characteristics of alcohol exposure

Alcohol is a teratogen which is defined as a substance that induces a developmental malformation in a fetus. A teratogen can produce consequences at four levels: 1) functional teratogenesis 2) growth deficiency 3) malformations and 4) death (Streissguth and LaDue 1987). A dose-effect relationship is postulated to exist although the dose required to produce a certain effect varies; higher doses are associated with more detrimental consequences (Vorhees 1986). Maternal alcoholism increases the rate of spontaneous abortion about two-fold (Abel and Sokol 1988). This is consistent with data from animal models demonstrating that resorption rates increase if rodents and monkeys are fed diets containing ethanol (Abel and Sokol 1988). Stillbirths, on the other hand, do not appear to be associated with ethanol intake (Abel and Sokol 1988). Malformations secondary to ethanol are noted in the skeletal, neurological, cardiovascular (seen in about 50% of the affected fetuses), renal, and possibly immunological systems (Burd and Martsolf 1989) (see Table I, p. 41).

Growth deficiency is often a consequence of *in utero* alcohol exposure. Abel and Sokol note that the average weight of 300 neonates with FAS is 2000g as compared to the median weight of 3300g in the United States (Abel and Sokol 1988). Of note, is the finding that beer drinkers deliver infants who weigh less than those born to women who drink other alcoholic beverages (Abel and Sokol 1986). This finding may be a consequence of such epidemiologic factors as the socioeconomic status of those who drink beer (Abel and Sokol 1986). In addition, length and head circumference measurements are also decreased. Postnatally, these children fail to achieve the same growth as their unexposed peers. A recent study examining 61 patients diagnosed with FAS or fetal alcohol effects (FAE) between five and twelve years ago demonstrates that

height and head circumference remain about two standard deviations below the mean, although their weights are closer to the average (Streissguth et al. 1991).

Functional teratogenesis, which includes both behavioral and intellectual dysfunction, is the most detrimental effect of alcohol on the surviving fetus. Behavioral disorders are noted as early as the neonatal period with affected newborns exhibiting sucking difficulties, jitteriness, opisthotonos, hyperacusis, hypertonia, irritability, and occasional seizure activity (Burd and Martsolf 1989). Older infants have disturbed sleep-wake cycles, poor visual recognition, slow motor development, hearing difficulties, and abnormal language development. Comprehension of language is affected less severely than is speech production which includes articulation difficulties, echolalia, and perseveration (Streissguth and LaDue 1987). These children also tend to score lower on the Bailey developmental scale (Abel and Sokol 1986). Behavioral disorders in older children include hyperactivity (present in about two-thirds of those with FAS), attentional deficits, abnormal eye-hand coordination, and problems with visual perception. As adolescence approaches, their poor social judgment and lack of impulse control lead to social maladjustment (Streissguth and LaDue 1987).

If the mother stops drinking during pregnancy, these effects are less pronounced as shown by Warren and Bast (1988). They retrospectively studied 103 neonates who did not have overt manifestations of FAS and divided them into three groups (Warren and Bast 1988). Group I was comprised of infants whose mothers abstained from drinking, group II contained infants whose mothers drank on average 12 ounces per week but stopped by the second trimester, and group III consisted of mothers who drank 12 ounces per week throughout pregnancy. Examinations of the infants at 3 days, 30 days, and 6 months post partum showed differences in motor performance, reflexive behavior, and autonomic control. The infants who were exposed to alcohol throughout pregnancy were most affected while the infants whose mothers did not drink were the least affected. As with any other teratogen, these effects are not seen in all infants who have been exposed

to alcohol and the degree of the effect is variable. The individual factors which determine the final outcome, whether genetic, environmental, or a combination of both, are currently not well understood.

Mental retardation, which is another aspect of functional teratogenesis, is common in children with FAS who have a mean intelligence quotient (IQ) of 65 with a range from 15 to 105 (Streissguth and LaDue 1987). In a series of 20 patients with FAS, Streissguth et al (1978) note a direct relationship between IQ and severity of the dysmorphogenesis, i.e., the more severe the dysmorphogenesis or the greater the amount of growth deficiency, the more severe the intellectual impairment (Streissguth, Herman, and Smith 1978).

The intellectual handicaps which *in utero* alcohol exposure produces are not mitigated with time. A follow-up study of the first 38 patients diagnosed with FAS or FAE, performed between the ages of 12 and 40 years, demonstrates a mean verbal IQ of 63 and a mean performance IQ of 77 as determined by either the Wechsler Intelligence Scale for Children-Revised or the Wechsler Adult Intelligence Scale-Revised (Streissguth and LaDue 1987). These patients also exhibit significant delays in their adaptive living skills and socialization skills according to the Vineland Adaptive Behavior Scales (VABS). In a recent follow-up study of 61 FAS patients, behavioral and social skills as measured by VABS continue to be maladaptive (Streissguth et al. 1991). Overall, 62% of patients have a "significant" level of maladaptive behavior and 38% have an "intermediate" level. These patients perform best on the daily living skills section achieving a mean test level of 9 years at a mean chronological age of 17 years. The mean IQ is 66 and only 6% of patients are able to attend regular classes. None of the older patients are independent with regards to housing or income. These studies demonstrate that the severe intellectual and behavioral consequences of FAS are not ameliorated with age.

Epidemiology

FAS is the leading preventable cause of mental retardation. Approximately 60% of American women drink alcohol and about 4% are chronic alcoholics (Abel and Sokol 1988). Evidence suggests that about 5% of all congenital anomalies may be attributable to the effects of ethanol. The prevalence of FAS is estimated in the United States to be approximately 2.2/1000 live births, although the rates differ dramatically depending upon the population studied (Abel and Sokol 1988). Although FAS is seen among women of all racial backgrounds, the prevalence tends to be higher in areas where the majority of mothers are either black or Indian or are of low socioeconomic status. Among the subset of women who abuse alcohol, the prevalence of FAS is 59/1000. The percentage of infants with alcohol effects increases with greater amounts of maternal drinking (Hanson, Streissguth, and Smith 1978).

The Cleveland Fetal Alcohol Study attempted to address the issue of who was more susceptible to producing a child with FAS (Sokol, Ager, and Martier). In this study, 8331 consecutive women were screened at the first prenatal visit. Screening interviews included the Michigan Alcoholism Screening Test (MAST), recollection of information about the daily alcohol intake for a two week period, and also recollection of nutritional habits and drug use. At each interval prenatal visit, the women were questioned about their daily drinking histories for the antecedent two week period. Within 72 hours of birth, the infants were weighed, measured for length of torso, head circumference, palpebral fissures, and examined carefully for any possible alcohol related birth defects. Twenty-five FAS-positive infants were born and fifty non-FAS babies, determined by the births preceding and succeeding that of the FAS-positive infants, were selected to serve as controls. The mothers in the FAS group were older, more likely to be black, and had a higher gravidity and parity. The mothers of the FAS children had higher MAST scores, a greater number of reported drinking days, greater intake of alcohol per day, and a higher proportion of their alcohol intake from beer. Analysis of these factors revealed that about two-thirds of the variance could be explained by the following four factors: high

proportion of drinking days, positive MAST score, black race, and high parity. Black race was found to increase the risk about seven times after adjusting for the other three factors suggesting a genetic predisposition. Susceptibility based on genetic variation has been shown in mice as different strains have different blood alcohol levels after being fed equivalent amounts of ethanol (Abel and Sokol 1986). Thus, it is possible that those of the black race are at a greater risk of obtaining higher blood levels and therefore being more at risk to produce children with FAS; although, there have not been any studies in support of this idea.

Abel and Sokol (1986) attempted to verify parity as a factor in susceptibility to FAS (Abel and Sokol 1986). A group of rats that had mated three times was contrasted to a nulliparous group. Rats from the multiparous group were mated a fourth time and those from the nulliparous group were mated for the first time. During the mating, they received either alcohol, nothing, or a vehicle. The rats born to primiparous females weighed about 0.5g more than those born to multiparous females. In addition, they found that the pups born to the alcohol fed females weighed less. However, there was no interaction between these two variables. Statistical analysis was not done on these numbers, so the significance of a 0.5g difference is unclear.

Placental transport of ethanol

Despite the high prevalence of FAS, ethical reasons prevent human studies on the absorption of alcohol and its variable transfer across the placenta, although one study did examine this (Brien et al. 1983). Brien studied six gravid subjects, who entered the hospital for a voluntary abortion in the early second trimester, and administered 0.3g/kg of ethanol prior to each abortion. The maximum maternal blood ethanol concentration varied from 0.23 to 0.73 mg/ml, and the time required to reach this maximum level ranged from 15 minutes to one hour. A variable period of 15 to 45 minutes was required before ethanol could be measured in the amniotic fluid; after 1.5 to 2.5 hours, the

maximal ethanol concentration of 0.09 to 0.31 mg/ml was attained. Acetaldehyde, on the other hand, was measurable only in the amniotic fluid of one and in the maternal blood of four subjects. After 3.5 hours, ethanol continued to be measurable in amniotic fluid, whereas it was not detectable in maternal blood. Thus, this study shows that maternal absorption and transfer of ethanol across the placenta is variable as is acetaldehyde production. In addition, it suggests that the fetus is exposed to ethanol longer than is the mother; thus, even after binge drinking, the fetus is exposed for a longer period of time than one would predict from the maternal blood ethanol level.

Animal studies

With animals, the amount of alcohol delivered can be controlled; therefore, they have been used to evaluate the critical time and pathophysiology of alcohol teratogenesis. Alcohol has been shown to produce neurological defects with exposure as late as the third trimester (Diaz and Samson 1980). Diaz and Samson (1980) examined the effects of alcohol exposure in rats during the immediate postnatal period, which is equivalent to the third trimester in humans. Intragastric nasal cannulas were used to feed ethanol-milk formula or milk formula alone to rat pups on postnatal days 4-7. On each day, the rats were given a battery of tests including "righting", negative geotaxis to a 30° slope, free fall righting, and cliff avoidance. The animals who were fed ethanol appeared sedated and had impaired performance on all reflex tests, a finding which persisted for days after the ethanol exposure. At postnatal day 17, the control and experimental pups were performing equally on the "righting" and cliff avoidance tests, but the experimental group continued to have difficulty with the free fall righting and negative geotaxis, which require the greatest motor coordination. On postnatal day 40, the rats were sacrificed and various measurements of the brain were obtained. The brains of rats from the ethanol-fed group weighed 19% less than the control ($p<.01$) and had statistically smaller cerebellums and cerebral hemispheres. Thus, Diaz and Samson concluded that ethanol exposure even

late in gestation can effect neurological development including the production of microcephaly.

A mouse model has been used to study the effects of brief alcohol exposure early in gestation (Sulik, Johnston, and Webb 1981). Sulik et al. injected C57BL/6J female mice with a solution of 25% ethanol (0.015 ml/gm maternal body weight) four hours apart on the seventh day of gestation. On day 7, the mouse embryos undergo formation of the mesoderm which is responsible for induction and maintenance of the neuroepithelium. One week after injection, the mothers were sacrificed and the embryos examined. The incidence of embryonic resorption in the experimental group was 18% as compared to 10% in the control litter. The most readily identifiable malformations in those who were given ethanol were microophthalmia, coloboma of the iris, and short palpebral fissures. These infants also had abnormal development of the nasal processes, philtrum, and upper lip, which are areas derived from the embryonic frontonasal prominence, lateral nasal processes, and medial nasal processes. In addition, brain size was reduced in the ethanol treated pups. Scanning electron microscopy (SEM) revealed bleb formation, consisting of cytoplasmic and nuclear material, on the neuroepithelium. Two embryos were exencephalic or anencephalic which is thought to be secondary to the neuroepithelial changes seen in some pups. This study demonstrated that exposure to ethanol or its metabolites could have a profound effect during a time period equivalent to the third week of human gestation. These abnormalities seen in mice were consistent with the craniofacial abnormalities seen in humans. In a subsequent study, the time of the initial injection was either at 6 days 20 hours, 7 days 0 hours, or 7 days 4 hours (Sulik and Johnston 1983). The group which was initially injected at 7 days 0 hours exhibited the greatest craniofacial defects, so tissues from this group were examined with SEM. Samples obtained 24 hours after the initial exposure revealed a reduction in the size of the neural plate, especially in the region of the forebrain, which would be expected to result in abnormal brain and eye formation. SEM analysis of embryos later in development

revealed that the medial nasal prominences, which contribute to formation of the philtrum and portions of the midface, are closer to the midline and are smaller in size as compared to the controls. Both of these studies showed alteration in craniofacial development following acute alcohol exposure early in gestation, but whether it is alcohol or a metabolite or both which caused these anomalies is unknown.

Webster et al attempted to address the question of the effects of acetaldehyde, a metabolite of ethanol (Webster et al. 1983). They injected or fed a group of mice alcohol (2.9 g/kg), injected a second group with acetaldehyde (0.32g/kg), or injected a third group with a combination of disulfiram (aldehyde dehydrogenase inhibitor) followed later by alcohol. The disulfiram was expected to produce a consistently high level of acetaldehyde. Two injections were given four hours apart on either days 7, 8, 9, or 10 of gestation. The alcohol produced variable defects dependent upon the day it was given and the resultant blood alcohol concentration. Alcohol given on day 7 produced craniofacial and neural tube defects, whereas, alcohol treatment on day 9 or 10 resulted in limb defects. The most common limb defects were reduction of forelimb and absence of the fourth or fifth digits. The acetaldehyde-treated groups demonstrated a lower number of abnormalities than did the alcohol groups but slightly more than the control group. The mice which were given disulfiram also showed a low incidence of malformations. This study suggested that acute ingestion of alcohol, or binge drinking, can produce malformations in the fetus, but it did not settle the argument about the teratogenicity of acetaldehyde since the acetaldehyde-treated groups experienced malformations but did not differ significantly from controls. The experiments with disulfiram were not different from those in which only alcohol was administered; thus implying that the acetaldehyde effect was minimal. However, since the teratogenic effects of disulfiram have not been investigated in the mouse, these results could not be interpreted.

The effects of acetaldehyde have been investigated more thoroughly by O'Shea and Kaufman. They injected either a 1% or 2% solution of acetaldehyde into the tail of

pregnant female mice and compared their offspring to control offspring from mothers who received a saline injection (O'Shea and Kaufman 1979). The number of resorptions was higher in the acetaldehyde-treated mice with a 2% injection solution producing the greatest effect ($p<.05$). Embryos who were treated with 2% acetaldehyde also showed developmental retardation as they did not adopt the fetal position as readily as controls. The crown-rump length was inversely associated with the concentration of acetaldehyde. Neurologic anomalies, namely failure of the anterior or posterior neuropore to close, were detected in embryos treated with either acetaldehyde or ethanol. Two embryos out of 122 showed cardiac anomalies. They concluded that acetaldehyde can cause some effects of FAS including death (resorptions), neurological abnormalities, growth retardation, and developmental delay. In a subsequent study, O'Shea and Kaufman (1981) demonstrated that injections given on the sixth day produced defects in the low cervical and high thoracic openings while injections on the seventh day produced hindbrain and midbrain malformations (O'Shea and Kaufman 1981). Examination of the neuroepithelium by scanning electron microscopy revealed an irregular cell surface with cells connected by spiny processes. The cells were disorganized with loss of their radial orientation. Some cells had small protrusions which may represent processes that were extruded from the cells.

Profound neurological impairment including mental retardation is one of the most devastating findings in FAS. The hippocampus, which is thought at least partially to contain the faculty of memory, has been implicated as a target for ethanol in the developing fetus. West et al. studied the organization of the hippocampus in rat pups whose mothers were fed a 35% ethanol diet and he noted a reorganization of the mossy fibers (West, Hodges, and Black 1981). Notably, although only one of six rats manifested external anomalies, they all still had the altered mossy fiber structure. Wigal and Amsel also studied hippocampal structure in four groups of rats: control, prenatal alcohol exposure, postnatal alcohol exposure, and combined pre- and post-natal alcohol

exposure. (Wigal and Amsel 1990). From postnatal days 19-21 various behavioral tests were performed after which the animals were sacrificed and the hippocampus examined on postnatal day 21. Prenatal alcohol exposure was associated with a decreased pyramidal cell density in the CA1 region and a decreased mature granule cell density in the dentate gyrus. The density of the CA1 region correlated directly with the rat's ability to learn, i.e. the alcohol-exposed rats with less pyramidal cell density had a more difficult time learning to perform a task. Postnatal alcohol exposure resulted in an increased density of the CA4 region which is thought to have been secondary to hypertrophy of granule cell axons. Thus, the brain appeared to undergo reorganization during the rat postnatal period which is equivalent to the third trimester of human gestation.

A great deal of *in vivo* animal work has been done, but *in vitro* studies are scarce. *In vitro* studies are advantageous because one can control the amount of substance in the culture medium without concern for effects of metabolic products. In addition, the variable absorption in the gastrointestinal system or the variable transfer across the placenta is not a factor. Brown et al. (1979) used the post implantation rat embryo culture technique to grow rat conceptuses during the period of organogenesis in two different concentrations of ethanol and to compare them with a control group grown in culture media for 48 hours (Brown, Goulding, and Fabro 1979). Embryos cultured in alcoholic media demonstrated a significant dose response reduction in the crown-rump length and head length ($p<.01$). The yolk sac and placenta did not differ much in size as compared to controls. Also, the higher dose ethanol-treated embryos had a reduced amount of total DNA and total protein. This study supported the hypothesis that alcohol alone could produce the malformations associated with FAS, but it did not rule out the possibility that acetaldehyde also has an effect.

Campbell and Fantel (1983) studied the effects of alcohol and acetaldehyde using the same culture technique for a 25 hour culture period (Campbell and Fantel 1983). The acetaldehyde concentrations ranged from 5 to 100 mm which were in the range of

physiologic amounts since it has been shown that chronic alcoholic men can attain a mean blood acetaldehyde level of approximately 25mm with a range from 5 to 50mm (Majchrowicz and Mendelson 1970). The highest concentration was almost uniformly lethal with only 1 of 23 embryos surviving. The lowest concentration had no observable effect. In a dose-dependent fashion, the intermediate concentrations produced decreases in measurements of growth and development. At 75µm, the decrease in total body size reached statistical significance. The decrease in head length size reached statistical significance at an acetaldehyde concentration of 25µm; thus it appears to be more sensitive than total body growth. The ethanol-exposed groups did not have a significant reduction in size. As shown in the study mentioned previously, ethanol effects were seen after 48 hours in culture, thus, the 25 hour culture period in this study may have been insufficient to produce the effects. This study implied that acetaldehyde is also capable of producing the teratogenic effects seen in FAS and requires lower concentrations and shorter incubation times as compared to alcohol.

Threshold

The animal investigations have not determined the threshold at which alcohol exposure produces teratogenic effects. Ernhart et al. (1987) attempted to elucidate the critical period and threshold for alcohol's teratogenicity by studying 359 mother-infant pairs who were divided on the basis of scores on the MAST questionnaire (refer to section of Questionnaires p. 13 for a more detailed explanation of MAST) (Ernhart et al. 1987). At each succeeding visit, the women were asked to recall their daily alcohol intake divided into the categories of beer, wine, and liquor. Only 139 of these women registered prior to the end of the first trimester, so for the remainder of the women only the amount of alcohol per day during the second trimester was used for analysis. Another comparative measurement used was the embryonic alcohol exposure which was determined by the following equation: (0.12 * MAST score) + (0.67 current absolute

alcohol per day) + .08 (Moron et al. 1985). An anomalies tally, which was was divided into craniofacial anomalies and other general anomalies, was used to compare the MAST-positive and -negative infants. There was a statistically significant increase in the incidence of anomalies in the MAST-positive group at $p<.001$ for the craniofacial and $p<.05$ for the general category. It is important to note that if one looks only at each individual anomaly then the difference between the positive and negative groups was not obvious, which reinforces the fact that a constellation of anomalies is required for diagnosis. In the MAST-positive group, the incidence of craniofacial anomalies was significantly related to the absolute amount of alcohol per day and the proportion of "drinking days" during the first trimester, but this was not the case for the other anomalies. The calculated embryonic exposure accounted for most of the variance between the tallies of the MAST-positive and -negative groups; thus, suggesting that the critical period is early in the first trimester. They also demonstrated that the abnormalities, especially the craniofacial ones are related in a dose response manner with >3 ounces of absolute alcohol per day increasing the risk for FAS.

Questionnaires

As one can see from the above studies, there is little definitive data on the pathophysiology of FAS; therefore, physicians need a reliable method of screening expectant mothers for alcoholism. It is difficult to determine the maternal alcohol history since many patients are not accurate in their assessment or recall of the amount they drink. This factor compounds the problem of a lack of an accurate prenatal diagnostic test for FAS, since a physician is not able to determine which patients are at risk for bearing children with FAS. Several questionnaires have been devised to determine the risk of a patient for alcoholism. The Michigan Alcoholism Screening Test (MAST) was devised to provide health care personnel with an unbiased, structured form to detect alcoholism. The test consists of 25 questions which are each assigned a point score from

0-5; a total score of 5 or greater is considered to be a positive test for alcoholism (Selzer 1971). Selzer attempted to validate this scoring system in 1971 when he administered the questionnaire to five groups of people: controls, hospitalized alcoholics, those convicted of drunk driving, those convicted of drunk or disorderly conduct, and drivers with licenses under review. The scores on the test were then compared with records of various medical and social agencies and criminal records. Using this system, the MAST, which had a 5% false positive rate in the controls, was able to detect 59% of the people who had been arrested for drunk and disorderly conduct, 55% who had been arrested for drunk driving, and 98% of the people who were hospitalized alcoholics. Therefore, this test is good for detecting those with serious alcohol problems, i.e., have a need to be hospitalized, but it is not as accurate in detecting less severely affected individuals. In the gravid population, one needs to detect not only those who are serious alcoholics, but also those who one may not suspect since the amount of alcohol which produces an effect on the fetus during pregnancy remains to be determined. It is also of interest to validate the MAST against simply asking the patient if he or she is an alcoholic.

The CAGE test, introduced in 1970 by Ewing and Rouse, provides a simpler method than the MAST for detection of alcoholics (Ewing 1984). This test is a four question script which asks the following:

1) Have you ever felt you ought to **C**ut down on your drinking?
2) Have people **A**nnoyed you by criticizing your drinking?
3) Have you ever felt bad or **G**uilty about your drinking?
4) Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**E**ye-opener)?

This questionnaire is much shorter than the MAST and thus can more easily be incorporated into clinical practice. Compared to the MAST, the CAGE successfully detects 93% of those who drink excessively. Using the CAGE as a model, Sokol devised the T-ACE questionnaire, which replaces the question about guilt with one asking how

many drinks it takes to make one feel high (Tolerance). A positive response to the question of tolerance is defined as >2 drinks. The question of tolerance is thought to trigger less denial than the question of guilt (Sokol and al 1989). Sokol studied the utility of this questionnaire in a population of 971 gravid women with drinking histories and compared results to the MAST and the CAGE. The results show that a positive response to the tolerance question seems to increase the likelihood of risk drinking by 8.5% which is much higher than the likelihood of increased risk drinking with a positive response to any other individual question. In scoring the questionnaire, he assigns the tolerance question 2 points and a positive response to any of the other questions 1 point. A T-ACE score ≥2 is considered to be positive and hence to more indicative of a potential to be a risk drinker and thus jeopardizing the fetus. In comparison to the CAGE and MAST, the T-ACE has a higher sensitivity and specificity. Sensitivity for T-ACE is 76% as compared to 59% for MAST. The T-ACE is thus able to predict 7 in 10 women who are abusive drinkers (see Table II p. 42). This study only included those who admitted to drinking at some point during their life, thus a bias may have been introduced.

Waterson and Murrary-Lyon compared different methods of asking about alcohol consumption in a prenatal clinic (Waterson and Murrary-Lyon 1989). As part of the clinical history, the patients were asked quantity-frequency questions, a question on binge drinking, and the CAGE questionnaire. Later, they completed a detailed questionnaire which included frequency of drinking different types of alcohol, the CAGE questions, and the MAST questions. Their results showed that asking quantity-frequency questions along with a question on binge drinking was a quick and reliable method of estimating alcohol intake.

Of the questionnaires available to detect alcoholism, the MAST is the gold standard. After the MAST, the CAGE is the next most widely used questionnaire for detecting alcoholism. The principal advantage of the CAGE is its brevity without loss of sensitivity. Recently, the T-ACE questionnaire was introduced which has the advantages

of being concise and is superior to both the CAGE and the MAST as demonstrated by its higher sensitivity.

Diagnosis

Despite the voluminous amount of research and the rapid rate of discovery about FAS over the past fifteen years, the diagnosis of FAS remains problematic due to the lack of available definitive laboratory or other diagnostic tests. A more precise definition was adopted in 1980 by the Fetal Alcohol Study Group of the Research Society on Alcoholism in order to make the diagnosis of FAS more uniform. The following are the minimal criteria for the diagnosis of FAS with symptoms from each of the following areas required for diagnosis (Cooper 1987). If defects are noted in only one or two of these categories, then the diagnosis of fetal alcohol effects (FAE) can be made (Cooper 1987); although, this definition is not strict.

1) Growth retardation: prenatal and/or postnatal with weight, length, and/or head circumference below the 10th percentile.

2) Central nervous system: Signs of developmental delay, intellectual impairment, or neurologic abnormality.

3) Facial dysmorphology: Requires two of the following three signs: a) microcephaly with head circumference below the third percentile; b) microophthalmia or short palpebral fissures; and c) poorly developed philtrum, thin upper lip, or maxillary hypoplasia.

Although these criterion attempt to standardize the diagnosis, the clinician must still exercise judgement based on the overall appearance and behavior since a common unfailing characteristic does not exist. The facial characteristics are the most consistently seen defects and include short palpebral fissures, flattened nasal bridge, presence of

epicanthal folds, shortened nose, short indistinct philtrum, small chin, thin upper lip, and midface hypoplasia (see Figure I p. 48) (Streissguth and LaDue 1987).

The possibility of prenatal diagnosis based on laboratory tests has been investigated by Halmesmaki et al. They studied the utility of α-fetoprotein, human placental lactogen, and pregnancy specific ß1-glycoprotein as markers for FAS (Halmesmaki et al. 1986). α-Fetoprotein was chosen since it is produced by the fetal liver which may be damaged by exposure to ethanol and thus unable to synthesize normal amounts. Ethanol could damage the placenta, so the other two markers were chosen to assess placental function and to screen for significant placental damage. The cohort consisted of 35 women who drank throughout pregnancy and 14 women who were abstinent. Thirteen women gave birth to infants who were thought to have FAS, one of which was a stillbirth. Low α-fetoprotein predicted FAS in 59% of the cases with a sensitivity of 43% and pregnancy specific ß1-glycoprotein predicted 56% of the cases with a sensitivity of 60%. Human placental lactogen had no predictive value. While this study does not invalidate the use of maternal serum markers, their reliability does not justify their use as standard prenatal markers.

In 1984, Vitez et al attempted to apply a more rigorous requirement to making the diagnosis of FAS by devising a semiquantitative scoring system (Vitez et al. 1984). They studied 464 children born of alcoholic mothers (301 continued to drink throughout pregnancy and 163 abstained during pregnancy) and 464 children born of non-alcoholic mothers. They examined 60 traits and assigned each trait a score with a more negative score being equivalent to slower development. The features encompassed CNS deficits, growth parameters, craniofacial defects, and other assorted anomalies. The mean score of the 301 children whose mothers imbibed was -14.4 points with most of the scores in the range of -30 to +5 points. A number of children in this set scored below -30 points. For the group of 163 children whose alcoholic mothers abstained during pregnancy the mean score was -4.11 points with the majority falling between -15 and +10 points. The

matched control group of 464 children had a mean score of +1.97 with the majority in the range from -10 to +15 points. According to their scoring system, a child with a score of -30 or less was considered to have FAS, while a child whose score fell between -30 and -10 was suggestive of an atypical form of the syndrome (FAE). The group whose mothers were abstinent scored slightly lower than the control group although no statistical analysis was done. The abstinent group combined mothers who were alcoholics prior to pregnancy and abstained during pregnancy with those who did not become alcoholics until after pregnancy; thus, it is unclear why the abstinent group would score lower especially since two-thirds of the mothers in that group did not become alcoholics until after delivery. Further analysis of the subsets of women comprising the abstinent group may help to determine whether the difference in scores could be accounted for by excessive drinking prior to conception. It is also possible that the difference could be accounted for by the inaccuracies of studies which rely on self-reported estimates of drinking behavior.

Craniofacial measurements

The unique feature of FAS is the craniofacial dysmorphology. The women who abuse alcohol often simultaneously use other drugs including marijuana, cocaine, tobacco, etc. These other drugs are not associated with the craniofacial features seen in FAS. Graham et al (1988) studied the relationship between other drug use and the presence of features of FAS in 108 children of heavy drinking mothers as compared to 97 children of a control group of mothers (Graham et al. 1988). Children were judged on FAS characteristics by a dysmorphologist who was blinded to the maternal drinking histories. Logistic regression analysis demonstrated no significant association between nicotine, caffeine, and marijuana with the presence of facial features of FAS. However, alcohol was significantly related to certain facial dysmorphic features even after statistically adjusting for the use of other drugs ($p=.002$). Hanson et al. reported varying

maternal nicotine histories in 11 of 163 children diagnosed with FAS by clinical examination (Hanson, Streissguth, and Smith 1978). They also demonstrated that in the absence of alcohol use, heavy nicotine use was not related to the diagnosis of FAS. When the effects of nicotine were studied alone, there was a significant reduction in birth weight and length and an increase in perinatal death, but no reduction was found in head circumference or in catch up growth and development (Hardy and Mellitis 1972).

Rostand et al. (1990) recently reported the results of a blinded study to assess the significance of the craniofacial anomalies (Rostand et al. 1990). They interviewed 684 women and divided them into abstinent and light drinkers, moderate drinkers, or heavy drinkers based on the number of glasses of alcohol consumed per week prior to pregnancy. A morphological exam was performed on the infants with particular attention to a set of predetermined craniofacial characteristics. Children of the heavy drinkers had a statistically significant greater number of craniofacial characteristics compatible with FAS than controls. In addition, there was a trend towards lower birth weight in the infants born to alcoholics although this did not achieve statistical significance. This study confirmed the association between the classic facial features and FAS. Other studies have determined that the presence of these features at birth is a good predictor of the presence of dysmorphic features at 4 years of age (Graham et al. 1988). Graham et al compared 108 children born of mothers who were heavy drinkers to children born of a matched control group. A different examiner was used at 0 and 4 years of age. At 4 years, eight out of ten children thought to have fetal alcohol effects at birth were thought to have the dysmorphology, however, there was no single feature that was found to be diagnostic of fetal alcohol effects.

Jackson et al. (1990) attempted to better define the craniofacial features associated with FAS by studying six selected patients out of 25 who carried the diagnosis (Jackson and Hussain 1990). The six were selected based upon a score of -30 or less on the Vitez scale, a documented history of maternal alcohol abuse, and absence of endocrine

anomalies. The majority of the nineteen children were eliminated because the genetic mother was not available to obtain an accurate alcohol history. Only two of these patients lived in close enough proximity to the study center to allow for complete craniofacial and dental developmental evaluation. The patients underwent standard radiographs and a panorex. Both cases had a small head circumference, small head height, shortened palpebral fissures, flattened naso-orbital valley, short nose, flattened maxilla and zygomas, short upper lip, and small nasolabial angle. There was gross shortage of bone in the midface region. They noted that the small palpebral fissures were due to an overall reduction in orbital size. There was delay in dental development which paralleled the delay in bone development. They noted that many of the fifteen who were excluded from the study had the craniofacial features consistent with FAS, but there was no reliable evidence of maternal alcohol consumption. The authors concluded that the craniofacial features may be more important than previously recognized especially since an alcohol history is often difficult to obtain. Despite the limited sample size, these observations support the presence of clinically recognizable facial characteristics associated with FAS.

A more mathematical approach to defining the craniofacial morphology has been undertaken by Clarren and coworkers who analyzed photographs of 21 seven year old, alcohol-exposed children; two of whom had been previously judged to have FAS (Clarren et al. 1987). A control group of 21 children was also photographed. The photographs were shown to seven clinicians who were asked to rate the children on a scale of 1-5 with 1 being indicative of fetal alcohol effects and 5 being normal. Six of the seven clinicians were accurately able to determine the children who had been exposed to large amounts of alcohol; thus, substantiating the idea that the facies of affected children reflect the high levels of alcohol *in utero*. In the second portion of the study, a group of 23 facial landmarks was chosen and their coordinates were fed into a computer and digitized. A comparison of shapes of the various facial triangles that could be formed by these points was performed and statistical methods were fit to the data to determine if a difference in a

triangular shape existed among the groups. Statistically significant differences were noted in the measurement of interpupillary distance, midface length with respect to the size of the nose, small mandible, and flattened midface. This study is important because it shows that the facial changes remain characteristic as these children become older. This study also suggests that computer analysis accurately depicts facial features and thus may mimic what the clinician's eye sees.

Sokol and Chik (1990) computerized the neonatal facial morphometry associated with FAS. They took photographs of 97 neonates and entered the coordinates of specific landmarks into the computer (Sokol et al. 1990). The characteristic clinical features of FAS were statistically significantly associated with the presence of FAS as determined by computer analysis with a sensitivity of 75% and a specificity of 79%. Since the craniofacial features have been successfully computerized in children and in neonates, the next logical step is to perform analysis of the facial features of the developing fetus. The ultrasound machine provides similar information to a computer-based analysis, thus suggesting the possibility for a role of ultrasonography in the *in utero* diagnosis of FAS. Escobar et al. have shown that accurate, highly reproducible craniofacial measurements can be made as early as 16 weeks of gestation (Escobar et al. 1988); thus supporting the possibility of prenatal detection of FAS.

The literature suggests that there are characteristic craniofacial changes in FAS apparent in both animal and human models. Further, these changes can be detected during development in animal models and are conducive to digitization by computer analysis in human neonates and 7 year old children; thus, these changes appear to be consistent. Ultrasonography provides physicians a tool to study human development and has already proven useful in the prenatal detection of abnormal growth and of abnormal organ development. Ultrasonography can detect craniofacial features accurately at 16 weeks of gestation. In order to detect mothers who put their fetus' at risk for FAS, a highly sensitive questionnaire known by the acronym T-ACE has been developed.

Prenatal detection of FAS may allow for the mitigation of the severe neurological impairment seen in FAS, which is the most detrimental consequence of *in utero* alcohol exposure. As previously mentioned, animal studies show that exposure to alcohol leads to difficulty in motor coordination and to rearrangement of the hippocampal structure. Since human studies show that mothers who stop drinking during pregnancy produce children with fewer neurological deficits, the possibility of prenatal detection becomes more appealing. In order to investigate the feasibility of prenatal detection of FAS, we utilized the combination of the T-ACE questionnaire, which detects potential pregnant alcoholics, with ultrasonography, which accurately determines craniofacial and intracranial measurements during development.

METHODS AND MATERIALS

The idea for this study is the result of discussions among Drs. Sterling Clarren, Robert Sokol, and John Hobbins with Dr. Richard Viscarello becoming involved in the discussions later. My advisor, Dr. Richard Viscarello, and I completed the design of the clinical study and the questionnaire (see Appendix I, p. 50). I completed the pilot study to assess the feasibility of the design and the completeness of the questionnaire. During the study, the questionnaires were administered either by myself or by a trained interviewer. The ultrasonography was performed by trained ultrasonographers or by Richard Viscarello, M.D.. Ultrasonographic measurements determined from the pictures taken during the ultrasound were determined by myself with the assistance of Richard Viscarello, M.D.. I performed the data analysis including writing a computer program to divide the data into their appropriate categories and performing the statistical analysis.

The results published here are from data analyzed at the first data analysis point. In order for statistical significance, power analysis calculations assuming a prevalence of 20% and a confidence of 80% would require 2,620 patients.

Patient selection

From 1988-1990, the T-ACE questionnaire was administered by trained interviewers to women registering for prenatal ultrasounds at one of three sites: 1) Womens' Center at Yale-New Haven Hospital 2) Perinatal ultrasound unit at Yale-New Haven Hospital or 3) Gessler Clinic in Winter Haven, Florida. Those women with T-ACE scores ≥ 2 points (T-ACE positive) were considered to be the "at risk" group and the remainder comprised the control group (T-ACE negative). Information regarding tobacco and illicit drug use and other demographic information was obtained during the interview (see Appendix I for sample questionnaire, p. 50). Oral consent was obtained for participation as approved by the Human Investigations Committee of Yale University School of Medicine and all patients were protected by a Certificate of Confidentiality obtained from NIAAD.

Gestational age was determined by the reported date of last menstrual period and confirmed by early ultrasound. Women who were unsure of their last menstrual period were excluded from the study as were women with multiple pregnancies. Women who were known diabetics were also excluded due to their propensity for fetal macrosomia.

Ultrasound examinations

Three time periods were selected for interval ultrasonographic measurements.

16-19 weeks (Group I): This period, which is equivalent to early second trimester, was selected as it is the earliest time in which accurate and complete craniofacial measurements can be obtained in the fetus (Escobar et al. 1988). Although vaginal ultrasound allows visualization of the face at 10 weeks, all the facial features are not distinct and studies have not been performed to assess the accuracy of these facial measurements.

24-28 weeks (Group II): This period, which is the end of the second trimester, allows possible detection of anomalies prior to the third trimester in which rapid neurological development occurs.

32-35 weeks (Group III): This interval ultrasound is during the mid third trimester allowing for possible detection prior to birth and thus, allowing for appropriate neonatal care.

Trained ultrasonographers performed comprehensive ultrasound examinations on each patient at each of the above intervals. All ultrasonographers were blinded to the results of the T-ACE screening. At each examination attempts were made to visualize a four chamber view of the heart. For various reasons, primarily missed appointments and late initial registration, some women did not receive all three ultrasounds. All ultrasound examinations were performed on either an ADR/ATL, Ultramark IX, and ADR/ATL Ultramark IVa, an Aloka Model 650, or an Accuson 128 scanner.

Craniofacial measurements

The craniofacial measurements studied were chosen to reflect abnormalities seen in children with FAS including microcephaly, hypertelorism, and mid-facial hypoplasia. These measurements included biparietal diameter (BPD), occipito-frontal diameter (OFD), outer-orbital distance (OOD), inner-orbital distance (IOD), mid-orbital to mid-upper lip distance (MOMUD), mid-orbital to mandible distance (MOMD), and outer orbital to mid-upper lip distance (MFT) (see Figure II, p. 49). Head circumference was calculated from BPD and OFD using the formula for an ellipse: (Ott 1984)

$$\frac{\sqrt{BPD^2 + OFD^2}}{2} * \pi$$

In order to determine BPD and OFD an axial section was obtained. A coronal section was taken to determine the facial measurements.

Intracranial measurements

The intracranial measurements studied attempted to measure brain size in various dimensions as the children with FAS have mental retardation, microcephaly, and difficulty with fine and gross motor function. In animals and in autopsy specimens it has been shown that the brain has a reduced size during development. The measurements studied included transcerebellar diameter (TCD), the distance from the cavum septum pellucidum to the inner-table of the skull (C-IS), and the distance from the thalamus to the inner-table of the skull (T-IS) (see Figure 2, p. 49). Axial sections at the level of the cerebellum and at the level of the thalamus were used to assess these measurements.

Table III (see p. 43) illustrates which FAS characteristics are being targeted with these ultrasonographic measurements and which characteristics cannot be determined by ultrasonographic analysis.

Statistical analysis

Statistical analysis between T-ACE positive and negative groups was completed with the Mann-Whitney U test. Analysis comparing T-ACE positive to published means was done with hypothesis testing and the student's t-test. In order to determine the means of the published standards, the standards for the weeks in each of the groups were averaged. The level of statistical significance was chosen as $p < .05$.

RESULTS

We interviewed a total of 265 gravid women ranging in age from 16 to 43 years with a mean age of 26 ± 5.5 years. The mean gravidity was 3.0 ± 1.9 with a range from 0 to 13. Parity ranged from 0 to 7 with a mean of 1.2 ±1.2. The racial make up was 70.7% Caucasian, 21.4% Black, 7.3% Hispanic, and 0.6% Other. Overall, 30.1% of the women were T-ACE positive; thus constituting a risk of FAS to the fetus. In the Gessler Clinic and the Yale Ultrasound Unit, the majority of the patients were Caucasian. During the first few months of the study, the Gessler study site matched each T-ACE positive subject with a T-ACE negative subject; therefore, the percentage of T-ACE positive patients may be falsely elevated and we expect the percentage to decrease at the next data analysis point. In the Women's Center, the majority of patients were black and a large percentage of the patients are T-ACE positive. The data for each site is presented in Table IV (see p. 44).

Confounding variables which were studied include smoking history and illicit drug history as obtained from charts and from questioning. Of the T-ACE positive women, almost 63% were cigarette smokers and 56% admitted to illicit drug use. Nearly 9% of the "at risk" women were using alcohol, tobacco, and illicit drugs during their pregnancy. In contrast, 28% of T-ACE negative women were positive for tobacco use and 6% acknowledged the use of illicit drugs. Approximately 2.2% of T-ACE negative women were exposing their fetuses to a combination of ethanol, tobacco, and illicit drugs.

Craniofacial measurements (Data summary in Tables V, VI, VII, p. 45,46, 47)

Although 265 patients were interviewed, the number of ultrasounds is substantially less for several reasons. First, some women did not receive all three ultrasounds. Second, women missed appointments and either did not receive ultrasounds or the period of gestation in which the ultrasounds were performed did not coincide with the periods

we were studying. Third, at the time of analysis, some women had been interviewed but had not yet received any ultrasounds.

Group I: 16-19 weeks gestation

Group I consists of 51 patients with a mean gestational age of 17.7 weeks for T-ACE positive and 17.9 weeks for T-ACE negative women. As displayed in Table V, there is a trend for measurements of head circumference, inner-orbital diameter, mid-orbital to mid-upper lip distance, and outer-orbital to mid-upper lip distance to be smaller in those fetuses who are "at risk." However, only head circumference is statistically significant with $p=0.05$.

From the measurements we examined, published standards exist only for head circumference, inner orbital diameter, and outer orbital diameter (Mayden et al. 1982), (Hadlock et al. 1983). There was no statistically significant difference between the T-ACE positive women and the standards.

Group II: 24-28 weeks gestation

There are 57 patients in Group II. As in the T-ACE positive fetuses in Group I, the same measurements are found to be smaller in this group with the addition of mid-orbital to mandible distance. Although these differences are not statistically significant, head circumference is close with $p=0.07$.

Compared to the published means, head circumference and inner orbital diameter are statistically significant with $p<.01$ and $p<.05$ respectively. The difference in outer orbital diameter is not significant.

Group III: 32-35 weeks of gestation

Unlike the other two groups, the 25 patients in Group III have measurements in the "at risk" (T-ACE positive) group which were often larger than in the control group. But, mid-orbital to mandible distance, mid-orbital to upper lip distance, and outer-orbital to

mid-upper lip distance remain smaller in those "at risk," although they are not statistically significant. There is no significant difference between published means and T-ACE positive fetuses.

Intracranial measurements (Data summary displayed in Tables V, VI, VII, p. 45, 46, 47)

Group I: 16-19 weeks gestation

All three intracranial measurements studied are approximately equivalent in the T-ACE positive as compared to T-ACE negative at this age of gestation.

Of these parameters, only transcerebellar diameter has a published mean, and the T-ACE positive women did not differ significantly from it .

Group II: 24-28 weeks gestation

In Group II, all three intracranial measurements studied, i.e. transcerebellar diameter, thalamus to inner-table of skull, and cavum to inner-table of skull are smaller in the T-ACE positive fetuses. The transcerebellar diameter and the thalamus to inner-table of skull are statistically significant with p values of 0.003 and 0.03 respectively.

The transcerebellar diameter as compared to the population mean is statistically significantly smaller in the T-ACE positive with $p<.01$.

Group III: 32-35 weeks gestation

In Group III, the intracranial measurements are similar between those fetuses "at risk" and the controls except for the TCD in which the controls were larger although not statistically significant. The difference between the T-ACE positive and the population means for TCD is statistically significant though.

Other examinations

Each patient had a four chamber view of the heart visualized at one of the three ultrasound examinations; there were no cardiac defects seen in any patient. In addition, there were no skeletal or other organ anomalies seen.

DISCUSSION

The mechanism by which alcohol acts as a teratogen remains unknown, although several hypotheses have been proposed. It is suggested that alcohol can cause a reduction in amino acid and nutrient transport across the placenta, thus inhibiting fetal growth (Fisher and Karl 1988). This diminished transport can be secondary to ethanol's effects on the Na^+-K^+ ATPase which is shown to be impaired by as little as 60 mg/dl of alcohol (Fisher and Karl 1988). Ethanol is shown to impair the transport of such important nutrients as zinc, thiamine, and folate, which are required by the fetus for normal growth and development. Zinc is necessary for DNA synthesis. Interestingly, zinc is transported as a ligand with histidine; thus, zinc deficiency also may be due to decreased amino acid transport. Diminished placental transport is not the only mechanism since ethanol can also have a direct toxic effect on embryonic growth (Brown, Goulding, and Fabro 1979).

Fetal hypoxia also is proposed as a hypothesis (Hoyseth and Jones 1989). Since the liver requires as much as a one hundred percent increase in oxygen consumption during ethanol metabolism, oxygen deprivation in other tissues of the developing fetus can result. In addition, large doses of alcohol are shown in monkey to lead to a transient collapse of the umbilical vasculature, contributing to fetal hypoxia (Hoyseth and Jones 1989).

Increased levels of prostaglandins have also been proposed as a mechanism of teratogenesis in alcohol exposed fetuses since alcohol is shown to result in an increased level of prostaglandins secondary to stimulation of its release from tissues (Hoyseth and Jones 1989). High concentrations of prostaglandins result in increased levels of cAMP which decreases the rate of cell division.

A third possible mechanism of teratogenesis involves an alteration of hormone levels due to alcohol consumption (Hoyseth and Jones 1989). Women who give birth to infants with FAS are shown to have lower levels of estradiol and estriol throughout pregnancy. These women are also noted to have lower levels of progesterone and higher levels of

prolactin between the 16th and 24th weeks of gestation. The active mechanism by which these hormones may lead to FAS is not yet determined.

Since the mechanism of alcohol teratogenesis is not known, a safe level of alcohol consumption during pregnancy remains to be established making the early identification of problem drinking and its therapy essential components of prenatal care. The severity of the mother's alcoholism is shown to be the best predictor of the child's long term outcome (Burd and Martsolf 1989); thus, children of women who drink throughout pregnancy are at a higher risk for adverse alcohol related effects. This idea is supported by the follow up study of the first eleven FAS children which suggests that the three mothers who died of alcohol related causes were the ones whose children were the most severely affected (Streissguth, Clarren, and Jones 1985). Another study shows that women who discontinue drinking in the first trimester produce infants of normal length, weight, and head circumference as well as appropriate growth and development at an 18 month follow-up period (Burd and Martsolf 1989). Cognitively, children whose mothers stop drinking in the first trimester develop normally, but those whose mothers stop in mid-pregnancy are one to two standard deviations below the mean. The mothers who drink throughout pregnancy bear children whose cognitive development scores fall 2 to 4 standard deviations below the mean (Burd and Martsolf 1989).

Although reducing drinking early in pregnancy reduces alcohol related defects, it is not known with certainty in which trimester the most severe neurological damage is produced. In humans, it is known that from mid-gestation through the third postnatal year is the time of most rapid brain growth (Diaz and Samson 1980). Some animal studies point to the third trimester as being the most critical stage of neurological development. In rats, the first seven to ten days postnatally is equivalent to the third trimester in humans (Dobbing and Sands 1979). Rat pups fed an ethanol-milk mixture on postnatal days 4-7 demonstrate normal body growth whereas the brain growth especially cerebellar growth is significantly lower in the ethanol exposed rats (Diaz and Samson

1980). This result is interesting for two reasons. First, some FAS children have minimal or no physical FAS features, but they still have the neurological deficits. Secondly, children with FAS are noted to have defects in fine and gross motor function which is controlled by the cerebellum.

The hippocampus has been the most suitable region of the brain to study in detail because of its precise laminar organization and because the most is known about its pattern of development (West, Hodges, and Black 1981). In addition, the hippocampus is thought to play a role in learning and memory which is affected in FAS. Rat embryos exposed to alcohol during days 10-21 of gestation, the second trimester of human development, show a decrease in the dorsal hippocampus pyramidal neurons at 60 days of age (Barnes and Walker 1981). In addition, their study found that cerebellar development is slowed but not permanently altered by second trimester prenatal ethanol exposure. West et al. executed a study in which three groups of rats were exposed to alcohol during periods equivalent to the three trimesters in human development (West and Hamre 1985). For third trimester exposure, gastrostomy tubes were implanted on the first postnatal day and left in until the tenth postnatal day. This study failed to find any alterations in hippocampal development in rats exposed prenatally to ethanol. Those exposed postnatally showed aberrant production of pyramidal cells in the CA3 region and reduction of the cerebellar Purkinje cells. This study, unlike the study by Barnes, failed to demonstrate first or second trimester prenatal effects. One reason for this discrepancy is that the pregnant rats in Barnes' study consumed on average 15.5 $\pm$ 0.9 g/kg/day of ethanol whereas in Wests' study they consumed 10.8 $\pm$ 0.8 g/kg/day. The rats fed postnatally received between 7.0 and 7.5 g/kg/day; thus this suggests that the amount of ethanol needed to produce a harmful effect during the third trimester is less than during the preceding trimesters. Also, some of the effects produced during the second trimester can be compensated for if drinking is reduced during the last trimester.

The issue of absolute quantity of alcohol ingested versus maximal blood alcohol levels is addressed by Warren et al. (1988) using postnatal rat pups divided into two groups (Warren and Bast 1988). One group received 12 doses of alcohol daily whereas the other group received four doses, but the total amount administered to the two groups was equivalent. The animals with the fewer doses, which means they achieved the highest blood alcohol level, had the smaller brains for body size as compared to both the controls and the animals receiving 12 doses of alcohol. Thus, the idea that the third trimester can produce long lasting CNS injury is supported since the rats were fed during the period equivalent to the third trimester in humans. These results suggest that a higher peak dose may be more important than the total quantity ingested. Although some neurological damage is most likely produced in the first two trimesters, these studies strengthen the idea that the third trimester is an important and possibly the most sensitive time for the effects of ethanol on the developing nervous system. Therefore, detection of possible alcohol effects prior to the third trimester has the potential to reduce the severity of the mental deficits characteristic of FAS.

The preliminary results from our study indicate that craniofacial changes characteristic of those found in FAS may be detectable as early as 16 weeks *in utero* with most characteristics being more prominent by 24-28 weeks. Although the tendency is for most of the craniofacial measurements to be smaller in the "at risk" fetuses only the difference in head circumference reaches statistical significance by 16 weeks of gestation. At 16 weeks, the differences between the T-ACE positive and the standard means was not statistically significant. This could either be because it is not statistically significant and just appears so due to the small sample size or because the small T-ACE positive group is not large enough for statistical significance. As compared to the published means, the inner orbital diameter and head circumference are also statistically significant at 24-28 weeks. The small sample size could account for a greater statistical significance when comparing the T-ACE positive group to the standards as opposed to comparing them to

the T-ACE negative group. Throughout all three gestational ages, the outer orbital distance is approximately equal in the T-ACE positive and negative groups. Both hyper- and hypotelorism have been suggested to occur in FAS (Gir, Aksharanugraha, and Harris 1989), thus these results may represent a combination of both occurring in the "at risk" population. The data must be cautiously interpreted because of the interaction of nicotine and illicit drugs with the effects of alcohol especially since drug and alcohol use often occur simultaneously. These other drugs can effect parameters such as growth, but thus far, only alcohol has been shown to produce the aforementioned craniofacial and intracranial features (Ernhart et al. 1987). A study on the effects of nicotine on the fetus compared 88 children born to mothers who smoke with 88 controls. Infants exposed to nicotine *in utero* have decreased length and body weight at birth which is compensated for with time. A seven year follow up shows no difference between the two groups in intelligence. This is unlike FAS where the characteristics do not approach the mean with time (Hardy and Mellitis 1972) (Streissguth et al. 1991). With a larger sample size, it will be possible to perform multivariate analysis on our data to account for any effects which may be secondary to tobacco or illicit drug use.

The results of the early intracranial measurements are not yet conclusive, but the trend is toward smaller measurements at 16-19 weeks in the T-ACE positive women. The difference is definitely detectable by 24 weeks with transcerebellar and thalamus to inner skull distance being statistically significant. With the required sample size of approximately 2600, the abnormalities may be detectable earlier than 24 weeks.

Comparison of the T-ACE positive data to published population standards indicates statistically significant differences in transcerebellar diameter, head circumference, and inner orbital diameter in the 24-28 week range. This is consistent with comparison of T-ACE positive and negative women. At this data analysis point though, there are not enough subjects to confidently use the T-ACE negative group as the control. The published standards are a good baseline since they are determined from large studies.

Also, these standards are relied upon in obstetric patients as the expected means. Thus, in order to substantiate our T-ACE negative population as an accurate control group, it is important that the results which are statistically significant between the T-ACE positive and T-ACE negative group are also statistically significant between the T-ACE positive group and the population means. After this substantiation, we reliably will be able to use our T-ACE negative group as a control for the parameters where population means have not been determined and for future studies. It is encouraging that this study shows differences at 24-28 weeks since rat studies support the idea that detecting intracranial changes as late as 24-28 weeks may be adequate to prevent or at least to minimize serious mental impairment as significant neurological development occurs in the third trimester.

The data from third trimester ultrasounds does not show a significant difference between the T-ACE positive and negative groups. At present, the reason for this is unclear. It is more difficult to perform accurate facial measurements during the third trimester as the head engages. Another possibility, and probably the most likely one, may simply be an inadequate number of data points. Lastly, it is possible that some of the women may have reduced or stopped their drinking by the third trimester, so some of the craniofacial and intracranial effects that were measured at 24-28 weeks may have been mitigated. In the future, it will be important also to question the women on their drinking habits during the third trimester to control for these effects.

An accurate diagnosis of FAS cannot be made until the neurological development is assessed in the early childhood years. In addition, some children have FAE in which they may not have craniofacial changes but may have impaired neurological development which also will be detected in the early years of life. Therefore, it will not be known with certainty which infants are effected with FAS until a follow-up study is performed at regular intervals over the next few years in order to look at the social, emotional, and intellectual development of the children. Thus far, it appears that 2 of the T-ACE positive fetuses may have FAS, but others may later prove to have FAE. This gives us a

prevalence of FAS of 1 in 130 in our study which falls within the range seen in the population in the United States.

Even if fetuses at risk can be detected consistently with the combined use of the T-ACE questionnaire and ultrasonography, the physician must deal with the issue of altering the mother's drinking. Several studies have documented that supportive counseling can be beneficial in "at-risk" women. Halmesmaki has shown that it is possible for alcoholic women to reduce their alcohol intake (Halmesmaki 1988). He studied 85 pregnant women who abused alcohol and divided them into groups of either alcoholics, heavy drinkers, or moderate drinkers. The patients were counselled at 2-4 week intervals about the effects of alcohol on the fetus. The patients were urged to abstain from alcohol, but if they were unable to do so, then they were encouraged to at least decrease their alcohol consumption. The patients also had free access to social workers and psychiatrists. In addition, they could phone for counseling or simply to talk with someone whenever they felt the need. When patients did not come to their follow-up appointments, they were telephoned and persuaded to come. At each visit, an ultrasound examination and urine for alcohol levels were obtained. Overall, the results showed that 65% of the women lowered their alcohol consumption by 50%. Of the 36 gravid women who registered between 12 and 20 weeks, 94% reduced their drinking by at least half, as compared with only 54% of women who registered later. Those who received counselling after 32 weeks were unable to decrease their alcohol consumption. FAS was noted in 20 patients, while FAE was suspected in an additional 22 patients. Eighty-nine percent of the infants whose mothers were unable to lower their alcohol consumption were born with FAS or FAE, but only 40% of those whose mothers reduced drinking had features of FAS or FAE. Therefore counseling of alcoholic women may be efficacious if initiated early in pregnancy. However, the patients in this study who registered earlier may have been more motivated to abstain from alcohol during pregnancy.

Others have also documented success with intensive counselling for pregnant alcoholic women. Rosett et al. found that with counseling 67% of heavy drinking women were able to abstain or significantly reduce their alcohol consumption prior to the third trimester (Rosett, Weiner, and Edelin 1983) (Rosett, Weiner, and Edelin 1981). In addition, those who reduced their consumption delivered babies with more normal growth parameters. Their program consisted of an initial intake interview and detailed drinking history with a psychiatrist followed by a session with the psychiatrist and/or counselor occurring one to four times per month. If a woman reported drinking, the harmful effects of alcohol were reinforced. In counseling these patients, the researchers found that it was important to avoid criticism and feelings of guilt.

Larsson studied all women who attended one of the four Maternal Health Clinics in Sweden (Larsson 1983). The patients were divided into three groups based on the amount of alcohol consumed. Of women who were not "addicted" to alcohol, education about the adverse effects of alcohol was found to be sufficient to change their drinking habits. On the other hand, alcoholic women, defined as those who drank more than 125 g of pure alcohol per day, required intensive counseling in order to reduce their drinking. Information regarding the effects of how an alcoholic environment endangers the baby's development had the strongest effect on influencing drinking habits. The supportive environment was also an important component. The patients were provided free access to a social worker, a psychiatrist, and the Department of Social Welfare to aid in improving their domestic situation.

Another program, organized by Little et al., provided public education, a 24 hour crisis information line, adult treatment services, adult education, and assessment of the infants (Little et al. 1984). About 50% of the women enrolled in this program were able to abstain or significantly reduce their alcohol consumption prior to the third trimester with those who decreased their alcohol intake delivering healthier infants. The estimated cost of the project was approximately one million dollars which is equivalent to the cost

of providing care for one severely retarded child affected by FAS for a lifetime. Thus, the cost is minimal relative to the amount that might be spent without the program.

Although it would be ideal to give supportive counseling to every gravid woman, it simply is not feasible due to time and economic constraints. Each of the above described counseling programs met with the women a couple of times per month which requires a great deal of effort by the counselors. It would be impossible to do this with every woman who is pregnant. The evidence is convincing that even alcoholic women have the potential to stop or decrease their drinking habits before the third trimester. Evidence from laboratory animals and from women who have stopped drinking, shows that a significant amount of neurological damage can be done in the third trimester and damage done prior to the third trimester may be reduced if drinking is stopped or at least curtailed. Our study, shows that certain measurements are significantly different in "at risk" women late in the second trimester of pregnancy. Thus, if the women who have a combination of a positive T-ACE questionnaire and ultrasonographic measurements suspicious for FAS associated developmental anomalies could be placed in an intensive counseling group, their children could be helped prior to birth. In addition, early detection by the obstetrician would alert the pediatrician to a potential problem. Thus, the child could be watched closely for developmental delay and be put into an appropriate educational program early in life. It has been shown that children with FAS do better with early educational intervention (Streissguth et al. 1991).

The prospect that a large percentage of pregnant alcoholic mothers are able to eliminate or decrease their intake of alcohol makes the possibility of prenatal diagnosis of FAS more important. Currently, prenatal diagnosis of abnormalities is aided by ultrasonography, maternal serum markers, and chromosomal anomalies. Unfortunately the anomalies detected by these methods, such as Down's syndrome, spina bifida, or structural organ defects, are not preventable or alterable *in utero*. On the other hand, intensive counseling of the selected mothers determined by a prenatal diagnostic test for

FAS may lead to mitigation or even prevention of the severe neurological impairment seen in FAS. In this study, the possibility of prenatal detection of FAS is investigated through the combination of an assessment aimed at discovering potential alcoholic mothers, the T-ACE questionnaire, and a means of studying the development of facial features and intracranial growth, the ultrasound examination. The results thus far are encouraging as both craniofacial and intracranial measurements reach statistical significance at 24-28 weeks, although we need about 2600 patients for the results to be definitive. In conclusion, this study suggests that the prenatal detection of FAS is possible in the second trimester with the combination of the T-ACE questionnaire and prenatal ultrasonographic examination; thus, providing an avenue for secondary prevention of FAS.

TABLE I: Abnormal findings in infants born with FAS

Skeletal
Hypoplastic toenails
Shortened fingers
Radioulnar synostosis
Flexion contractures of the elbow
Camptodactyly of the fingers
Clinodactyly of the toes
Decreased flexion of the metacarpophalangeal joints
Hip dislocation
Spinal stenosis
Scoliosis
Pectus excavatum
Pectus carinatum
Polydactyly
Cardiac
Atrial septal defect
Ventricular septal defect
Hypoplasia of pulmonary arteries
Neurological
Microcephaly
Cerebellar dysgenesis
Corpus callosum agenesis
Neural tube defects- anencephaly, myelomeningocele
Renal
Renal hypoplasia
pyelonephritis
Painless hematuria
Immunological
Increased susceptibility to bacterial infection

TABLE II: Accuracy of tests available for alcoholism screening

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
MAST	36%	96%	29%	97%
CAGE	38%	92%	18%	97%
T-ACE	69%	89%	23%	98%

TABLE III: FAS characteristics: Which are detectable by ultrasonography?

Characteristic	Definitely detectable by ultrasonography*	Possibly detectable by ultrasonography*	Undetectable by ultrasonography
Growth retardation			
Prenatal	x		
Postnatal	N/A	N/A	N/A
Facial dysmorphology			
Microcephaly	x- HC		
Short palpebral fissures		x-OOD, IOD	
Epicanthal folds			x
Midfacial hypoplasia		x-MFT	
Short nose		x-MOMUD,MOMD	
Indistinct philtrum		x	
Micrognathia		x-MOMD	
Thin upper lip			x
Central nervous system			
Small brain size		x-T-IS,C-IS	
Tremulousness			x
Fine motor dysfunction		x-TCD	
Hyperactivity			x
Poor attention span			x
Mental retardation			x

*Abbreviations refer to measurements we hope will determine the corresponding characteristic. See text for abbreviations and explanations. The characteristics should be detectable at all three ultrasound periods in this study.

HC: head circumference
OOD: outer-orbital diameter
IOD: inner-orbital diameter
MFT: outer-orbital to mid-upper lip distance
MOMUD: mid-orbital to mid-upper lip distance
MOMD: mid-orbital to mandible distance
T-IS: thalamus to inner-table of the skull distance
C-IS: cavum septum pellucidum to inner-table of the skull distance
TCD: transcerebellar diameter

TABLE IV: Characteristics of women in study

	WOMEN'S CENTER (N=73)		YALE U/S UNIT (N= 62)		GESSLER CLINIC (N=130)	
	T-ACE positive (N=26)	T-ACE negative (N=47)	T-ACE positive (N=11)	T-ACE negative (N=51)	T-ACE positive (N=57)	T-ACE negative (n=73)
AGE (YR) ± SD	25.9 ± 4.7	23.5 ± 4.3	27.8 ± 5.2	26.9 ± 6.9	27 ± 5.9	26.8 ± 4.5
GRAVIDITY ± SD	3.4 ± 2.2	3.4 ± 2.2	5.0 ± 2.4	3.3 ± 2.1	2.2 ± 1.2	2.4 ± 1.2
PARITY ± SD	1.2 ± 1.2	1.4 ± 1.2	2.4 ± 2.4	1.2 ± 1.2	0.8 ± 1.0	1.1 ± 0.9
% CAUCASIAN	42	38	54	82	96	97
% BLACK	50	49	46	8	2	1.5
% OTHER	8	13	0	10	2	1.5
% POS CIGARETTES	54	38	36	8	N/A	N/A
% POS ILLICIT DRUGS	38	6	46	0	N/A	N/A

TABLE V: Comparison of T-ACE positive and T-ACE negative (16-19 weeks)

		16-19 WEEKS (N=51)		
	STANDARD MEANS	T-ACE POSITIVE N=19	T-ACE NEGATIVE N=32	Z-VALUE*
		MEAN ± SD (mm)	MEAN ± SD (mm)	
GA		17.7 ± .9	17.9 ± .8	
BPD		40.2 ± 4.0	41.3 ± 3.9	
OFD		49.3 ± 4.8	50.1 ± 9.3	
HC	142.5 (Hadlock et al. 1983)	139.7 ± 11.7	148.1 ± 11.7	1.37#
OOD	27.4 (Mayden et al. 1982)	29.0 ± 2.6	29.8 ± 3.2	1.01
IOD	10.7 (Mayden et al. 1982)	10.9 ± 1.7	11.6 ± 1.4	1.21
MOMD		20.6 ± 2.0	19.8 ± 3.3	0.53
MOMUD		9.8 ± 1.3	10.2 ± 2.0	1.57
MFT		18.8 ± 2.8	19.3 ± 2.8	0.15
TCD	17.5 (Goldstein et al. 1987)	18.2 ± 1.5	18.0 ± 1.4	0.15
C-IS		20.1 ± 2.2	20.3 ± 2.2	0.10
T-IS		34.5 ± 3.3	34.4 ± 3.1	0.12

*As determined by Mann-Whitney rank sum test
#$p<.05$

GA: gestational age
BPD: biparietal diameter
OFD: occipito-frontal diameter
HC: head circumference
OOD: outer-orbital diameter
IOD: inner-orbital diameter
MOMD: mid-orbital to mandible distance
MOMUD: mid-orbital to mid-upper lip distance
MFT: outer-orbital to mid-upper lip distance
TCD: transcerebellar diameter
C-IS: cavum septum pellucidum to inner-table of the skull distance
T-IS: thalamus to inner-table of the skull distance

TABLE VI: Comparison of T-ACE positive and T-ACE negative (24-28 weeks)
24-28 WEEKS (N=53)

	STANDARD MEANS	T-ACE POSITIVE N= 21	T-ACE NEGATIVE N= 32	Z-VALUE*
		MEAN ± SD (mm)	MEAN ± SD (mm)	
GA		25.7 ± 1.1	26.5 ± 1.2	
BPD		64.7 ± 4.1	66.2 ± 4.2	
OFD		82.2 ± 7.1	85.6 ± 6.2	
HC	242.5 (Hadlock et al. 1983)	231.2 ± 15.6	239.6 ± 15.0	1.82
OOD	44.2 (Mayden et al. 1982)	44.0 ± 3.8	44.5 ± 3.3	0.04
IOD	16.6 (Mayden et al. 1982)	15.7 ± 1.7	16.6 ± 2.1	0.87
MOMD		31.7 ± 2.7	34.2 ± 4.4	1.60
MOMUD		17.0 ± 1.7	19.2 ± 4.5	0.96
MFT		26.9 ± 2.9	27.4 ± 4.9	0.68
TCD	28.5 (Goldstein et al. 1987)	26.9 ± 2.2	29.6 ± 3.1	3.01#
C-IS		29.8 ± 5.8	32.3 ± 3.9	1.41
T-IS		49.0 ± 8.3	54.0 ± 4.3	2.19#

*As determined by Mann-Whitney rank sum test
#p<.05

GA: gestational age
BPD: biparietal diameter
OFD: occipito-frontal diameter
HC: head circumference
OOD: outer-orbital diameter
IOD: inner-orbital diameter
MOMD: mid-orbital to mandible distance
MOMUD: mid-orbital to mid-upper lip distance
MFT: outer-orbital to mid-upper lip distance
TCD: transcerebellar diameter
C-IS: cavum septum pellucidum to inner-table of the skull distance
T-IS: thalamus to inner-table of the skull distance

TABLE VII: Comparison of T-ACE positive and T-ACE negative (32-35 weeks)

	32-35 WEEKS (N=25)			
	STANDARD MEANS	T-ACE POSITIVE N=9	T-ACE NEGATIVE N=16	Z-VALUE*
		MEAN ± SD (mm)	MEAN ± SD (mm)	
GA		33.4 ± .90	33.4 ± 0.8	
BPD		83.7 ± 4.2	82.9 ± 3.5	
OFD		106.3 ± 5.1	104.9 ± 5.3	
HC	396.2 (Hadlock et al. 1983)	302.6 ± 16.4	297.4 ± 13.4	0.76
OOD	53.4 (Mayden et al. 1982)	53.2 ± 3.0	53.9 ± 1.9	1.20
IOD	19 (Mayden et al. 1982)	20.6 ± 2.9	20.0 ± 3.1	0.35
MOMD		41.8 ± 3.8	44.5 ± 3.1	1.19
MOMUD		19.8 ± 2.8	22.8 ± 3.0	1.41
MFT		30.2 ± 5.4	34.4 ± 3.6	1.87
TCD	39.6 (Goldstein et al. 1987)	36.6 ± 4.2	38.0 ± 2.2	0.15
C-IS		41.8 ± 6.2	41.9 ± 3.1	0.36
T-IS		65.4 ± 3.8	65.6 ± 4.9	0.05

*As determined by Mann-Whitney rank sum test

GA: gestational age
BPD: biparietal diameter
OFD: occipito-frontal diameter
HC: head circumference
OOD: outer-orbital diameter
IOD: inner-orbital diameter
MOMD: mid-orbital to mandible distance
MOMUD: mid-orbital to mid-upper lip distance
MFT: outer-orbital to mid-upper lip distance
TCD: transcerebellar diameter
C-IS: cavum septum pellucidum to inner-table of the skull distance
T-IS: thalamus to inner-table of the skull distance

Figure I: Characteristic facial features in fetal alcohol syndrome (Streissguth and LaDue 1987)

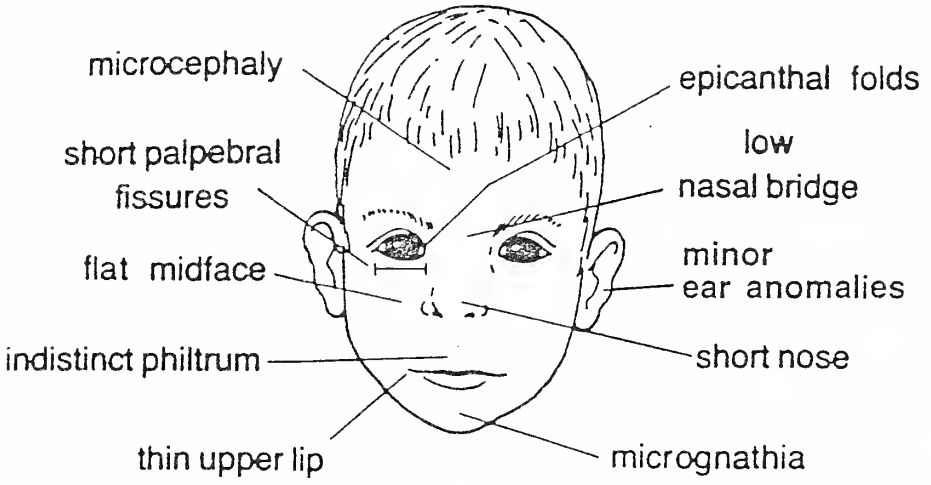
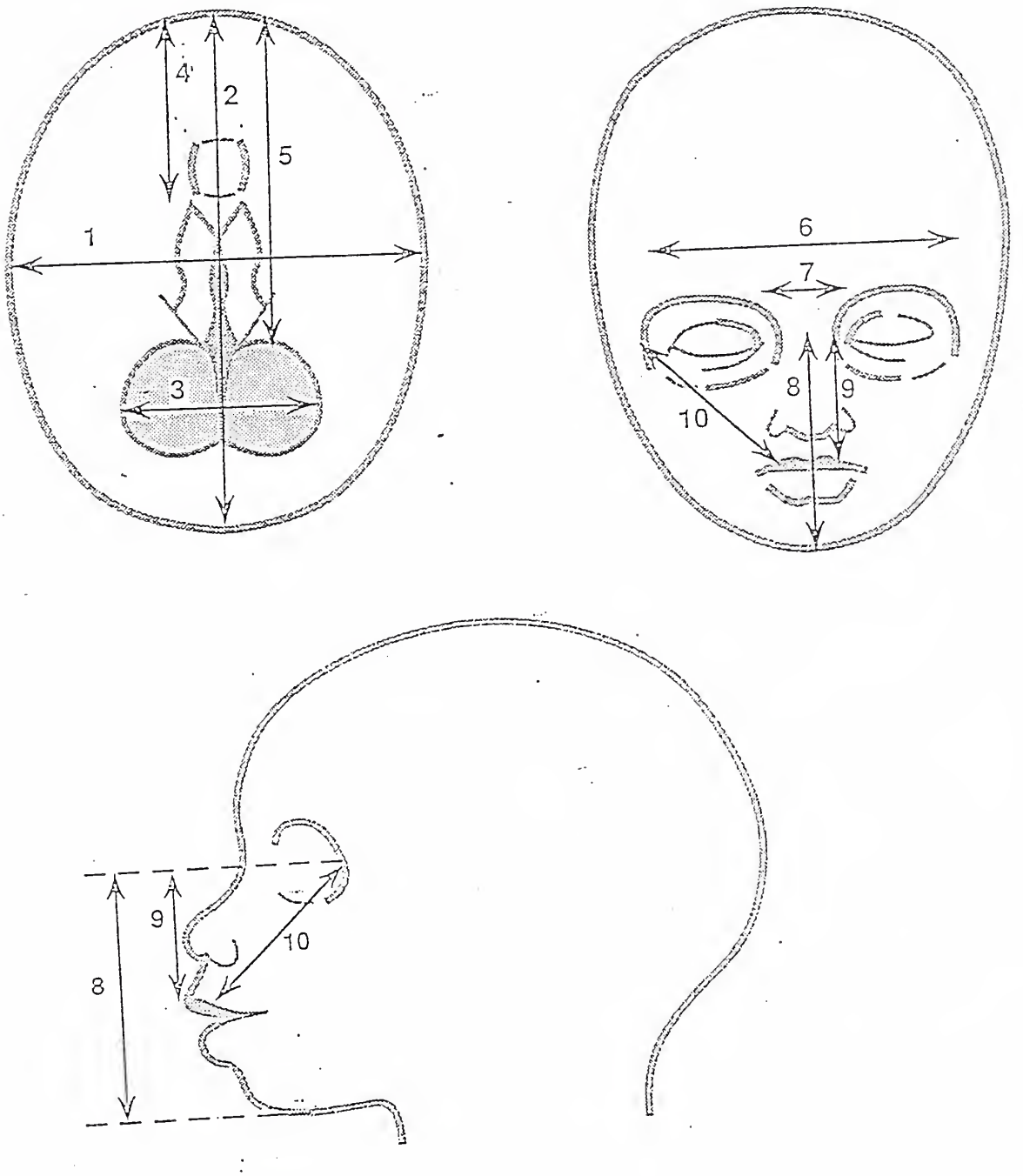


Figure II: Depiction of ultrasonographic measurements



1. Biparietal diameter (BPD)
2. Occipito-frontal diameter (OFD)
3. Transcerebellar diameter (TCD)
4. Thalamus to inner table of skull (T-IS)
5. Cerebellum to inner table of skull (C-IS)
6. Outer orbital distance (OOD)
7. Inner orbital distance (IOD)
8. Mid-orbital to mandible distance (MOMD)
9. Mid-orbital to mid-upper lip distance(MOMUD)
10. Outer orbital to mid-upper lip distance (MFT)

(Viscarello et al. 1991)

APPENDIX I

NAME _____ DATE _____
UNIT # _____ RACE _____ DOB _____
LMP _____ GA _____ AGE _____
G _____ P _____ sAB _____ tAB _____ ect _____ LC _____

ALCOHOL

1. How many drinks does it take to get you "high"? _____
2. Are you annoyed when friends suggest that you should alter your drinking habits? _____
3. Have you yourself felt the need to cut down on your drinking? _____
4. Have you ever had a drink to "cure" a hangover or to get started in the morning? _____
5. How many drinks can you hold? _____

T-ACE TOTAL SCORE _____

DRUG	ROUTE	AMOUNT, FREQ, & COST OF DRUG/WK Prepreg	Trim 1	Trim 2	Trim 3
COCAINE					
HEROIN					
MARIJUANA					
METHADONE					
VALIUM					
OTHER					

TOBACCO

Number of years smoking _____
Number of cigarettes per day while pregnant _____
Number of cigarettes per day prior to pregnancy _____

STD

HIV Hepatitis B Condyloma CC Trichomonas
Syphilis Chlamydia Herpes Other

FOOTNOTES

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